Reviewer's report

Title: Phenotypic profiling of CD8+ T cells during Plasmodium vivax blood-stage infection

Version: 1 Date: 18 November 2014

Reviewer: Sidhartha Chaudhury

Reviewer's report:

The authors carry out phenotypic profiling of CD8+ T cells from PBMC samples from subjects infected with P. vivax and show that the number of CD8+ naive and memory T cells are significantly decreased in patients with acute blood stage infection. Further analysis showed a decrease in central memory T cells and IFN-y producing memory T cells, and an increase in IL-10 producing memory T cells. The paper is generally well-written and thorough.

Major Compulsory Revisions:
None

Minor Essential Revisions:

1) Elaborate on the significance of absolute vs. relative changes in phenotypic profile of the CD8+ T cell response in terms of what it tells us about immunology and pathogenesis of P. vivax infection. In a number of measures, the absolute vs. relative numbers emphasize different results. For example, in absolute terms there is a large drop in IFN-y memory T cells in infected patients and very small increases in IL-10 and TNF-a T cells; in relative terms the increase in IL-10 and TNF-a T cells is much more pronounced. What is more important? The absolute number of IL-10 producing T cells or the relative proportion of IL-10 producing T cells?

2) The phenotypic changes in CD8+ T cells in patients with acute P. vivax infection is compared with the baseline phenotypic profile of non-infected controls. Discuss this baseline in greater detail - does the phenotypic profile of non-infected controls agree with previously published studies?

The memory T cell response in the baseline control seems overwhelmingly made up of IFN-y producing cells and central memory (CM) T cells. In infected subjects, is there a specific decrease in IFN-y producing and CM T cells? Or is there a general decrease in memory T cells, which from the baseline, happens to be mostly IFN-y producing and CM T cells.

3) Explain the significance of a correlation between IL-10 vs. IFN-y cells and IL-10 and TFN-a cells. A parsimonious explanation could simply be that even as the absolute magnitude of the responses varies from subject to subject, the relative or proportionate responses are consistent between them. Alternate
explanations could be that the IFN-y producing cells are the same cells that are producing IL-10. Please elaborate.

4) The authors show that plasma levels of IFN-y, IL-10, and TNF-a agree to some extent with the changes in relative population of IFN-y, IL-10, and TNF-a producing T cells. Are the authors suggesting that these T cells are responsible for the broad systemic changes in cytokine levels? Or that there is some common underlying mechanism that is responsible for both altering the phenotypic profile of the CD8+ T cell population and altering the plasma cytokine profile in infected patients?

Discretionary Revisions

1) Other studies measure the ratio of IFN-y producing cells to IL-10 producing cells and TNF-a producing cells to IL-10 producing cells as a gross measure of anti-inflammatory character of the T cell response. The authors might consider doing the same.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.